REMARKS

Entry of the foregoing amendments and favorable consideration of the subject application is respectfully requested in view of the following comments.

Claim 4 has been amended, claims 1, 2, 5, 6, 9, 11, 13, 15, 16, 18 and 19 have been cancelled and new claims 29-33 have been added. Accordingly, claims 4 and 29-33 are presented herein.

Claim 4, which was originally dependent from claim 1 and presented a specific form of the compound of general formula (I) of the present invention has been rewritten in independent form thereby presenting the specific form of the compound, or its pharmaceutically acceptable salts, as the preferred compound, and to incorporate the inclusion of HMG-CoA reductase inhibitors previously included in now cancelled claim 15 which was originally dependent from claim 4.

New claims 29-33 further define the invention by specifying the HMG-CoA reductase inhibitors (claim 29) as set forth in the specification at page 17, lines 3-5, the manner in which the serum cholesterol lowering agent or preventive or therapeutic agent for atherosclerosis of the present invention is administered (claim 30) as set forth in the specification at page 17, lines 22-24, the pharmaceutically acceptable additives and excipients includable in the serum cholesterol lowering agent or preventive or therapeutic agent for atherosclerosis of the present invention (claim 31) as set forth in the specification at

page 17, lines 24-26, the dosage range of the specific form of the compound and the HMG-CoA reductase inhibitor (claim 32) as set forth in the specification at page 18, lines 11-17, and the administration of the specific form of the compound and the HMG-CoA reductase inhibitor simultaneously or consecutively (claim 33) as set forth in the specification at page 18, lines 4-7.

Applicants respectfully submit that the foregoing amendment and new claims are fully supported by the application as originally filed and neither add new matter nor, in view of the nature of claims 29-33 as dependent from the narrower amended claim 4, expand the scope of the claims presented herein and that these amendments are properly in condition for entry at this time.

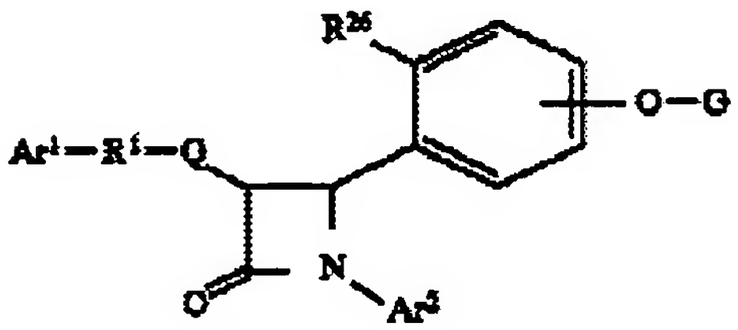
Applicants respectfully submit that the foregoing amendments place the application in condition for allowance.

Rejection of Claims Under 35 U.S.C. §103(a)

The Office Action rejects claims 1, 2, 4-6, 9, 11, 13, 15, 16, 18 and 19 under 35 U.S.C. § 103(a) as being unpatentable over Yumibe et al. (U.S. 5,756,470, May 26, 1998) and Tomiyama et al. (U.S. 2004/0063929, April 1, 2004, PTO-1449 submitted April 25, 2006, English equivalent of WO02/066464, published August 29, 2002). The Office Action states:

> "Yumibe et al teaches a combination of a cholesterol biosynthesis inhibitor and a β-lactam cholesterol absorption inhibitor for lowering cholesterol and treating or preventing atherosclerosis

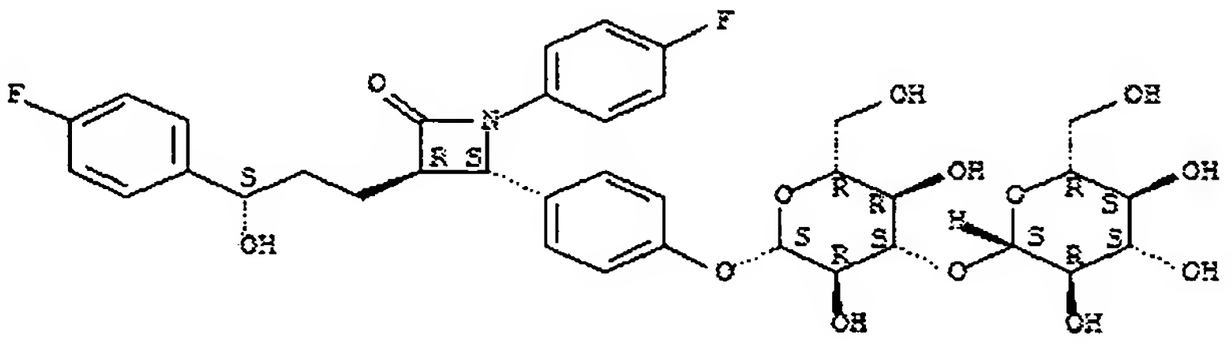
[see abstract]. The combination of a beta-lactam cholesterol absorption inhibitor and HMG-CoA reductase inhibitor results in a greater decrease in plasma cholesterol than either agent alone [column 2, lines 11-20]. Suitable cholesterol biosynthesis inhibitors include HMG CoA reductase inhibitors, squalene synthesis inhibitors, and squalene epoxidase inhibitors [column 2, lines 51-63 and claim 20]. The genus of compounds taught by Yumibe et al. is as follows [column 2]:



Wherein R^{26} is H or O-sugar, G is a sugar, and Ar^1 and Ar^2 are aryl or substituted aryl. Specific embodiments are claimed in claim 13 and include, among others, the following:

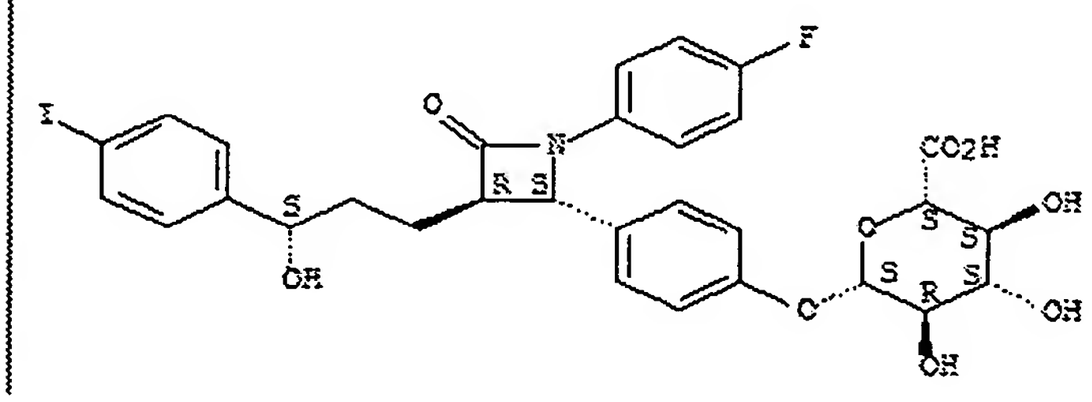
L2 ANSWER 3 OF 45 REGISTRY COPYRIGHT 2008 ACS on STN
RN 208259-77-2 REGISTRY
ED Entered STN: 09 Jul 1998
CN 2-Azetidinone, 1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-[(3-O-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]phenyl]-, (3R,4S)- (CA INDEX NAME)
FS STEREOSEARCH
MF C36 H41 F2 N O13
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



L2 ANSWER 11 OF 45 REGISTRY COPYRIGHT 2008 ACS on STN
RN 190448-79-4 REGISTRY
ED Entered STN: 27 Jun 1997
CN β-D-Glucopyranosiduronic acid, 4-[(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-(4-iodophenyl)propyl]-4-oxo-2-azetidinyl]phenyl (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H29 F I N O9
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

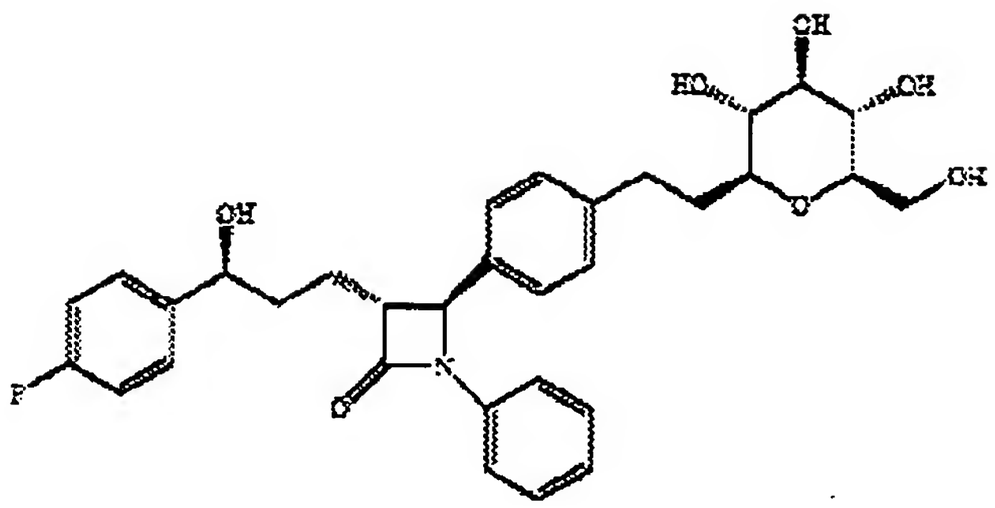


Pharmaceutical compositions comprising the compounds of Yumibe et al, and a cholesterol biosynthesis inhibitor are specifically claimed [claims 15 and 16].

The difference in the beat-lactams taught by Yumibe et al. and the instantly claimed beta-lactams is that the instantly claimed lactams comprise C-glycosides and those of Yumibe et al. comprise O-glycosides.

Tomiyama et al teach beta-lactam compounds which are useful as serum cholesterol lowering agents and which meet the limitations of the instant claims [see abstract and columns 2-3, and structures in columns 7-36]. Tomiyama et al. teach that O-glycoside bonds in beta-lactam-O-glucuronate compounds can be hydrolyzed in the small intestine, possibly reducing the activity of the compounds [column 1, lines 51-62]. Beta-lactams having a C-glycoside, which is stable to metabolism by glycosidase and hydrolysis, were prepared [column 2, lines 3-10]. One preferred compound, compound 56 [column 35], shown below, is the same compound as that which is recited in the instant claim 4:

56



Other preferred compounds include compound 37 [column 25], which is the same compound as that which is recited in instant claim 5.

Tomiyama et al. do not teach a combination of beta-lactam and cholesterol biosynthesis inhibitor.

It would have been obvious to one of ordinary skill in the art to prepare a cholesterol lowering composition of a cholesterol biosynthesis inhibitor and a β-lactam taught by Tomiyama et al. The combination of beta-lactam cholesterol absorption inhibitor and cholesterol biosynthesis inhibitor is already known in the art, as taught by Yumibe et al. Tomiyama et al. teach modified beta-lactmans which are ideal cholesterol absorption inhibitors with low incidence of side effects [column 1, line 65-column 2, line 2]. One of ordinary skill in the art could have substituted Tomiyama's modified beta-lactams for the beta-lactams in the combination taught by Yumibe et al. and would have predicted that the resulting composition would be effective for reducing plasma cholesterol levels and treating atherosclerosis.

Further, both cholesterol biosynthesis inhibitors and the β-lactams taught by Tomiyama et al. are known in the art for reducing serum cholesterol levels. It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose. In re Kerkhoven, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980)."

With regard to claims 1, 2, 5, 6, 9, 11, 13, 15, 16, 18 and 19, Applicants respectfully submit that cancellation of those claims herein renders the rejection thereof moot.

As to the rejection of claim 4, Applicants respectfully traverse the rejection thereof because a prima *facie case* of obviousness has not been established with respect to claim 4 as amended herein.

The Federal Circuit has ruled that a *prima facie* case of obviousness must establish: (1) some suggestion or motivation to modify the references; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all claim limitations. Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Feb. Cir. 1991); In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970). Applicants note that the "teaching-suggestion-motivation" test for obviousness is still applicable following the Supreme Court decision in KSR International Co. v. Teleflex Inc. 550 U.S. - , 82 USPQ2d 1385 (2007) and that there is no teaching, suggestion or motivation in the cited references to induce one of ordinary skill in the art to derive the present invention. A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

The examiner cites Yumibe, et al., U.S. 5,756,470 as teaching a combination of a cholesterol biosynthesis inhibitor, specifically HMG-CoA reductase inhibitors, and a beta-lactam cholesterol absorption inhibitor for lowering cholesterol and treating or preventing atherosclerosis. The examiner further cites Tomiyama, et al., U.S. 2004/0063929 as teaching the beta-lactam compound of the instant claim 4 as a useful serum cholesterol lowering agent which is stable to metabolism by glycosidase and hydrolysis.

However, the examiner acknowledges that Tomiyama, et al. do not teach the combination of the beta-lactam compound and a cholesterol biosynthesis inhibitor, much less the beta-lactam compound of claim 4 in combination with an HMG-CoA reductase inhibitor. Instead, the examiner contends, without reference to a specific teaching of the prior art, that such a combination would be obvious to one of ordinary skill in the art.

Claim 4 as amended herein presents a specific composition as a serum cholesterol lowering agent or preventive or therapeutic agent for atherosclerosis which comprises the combination of the beta-lactam compound 56 of Tomiyama, et al., and an HMG-CoA reductase inhibitor. This combination displays a significant pharmacologically synergistic effect with respect to the lowering of serum cholesterol that is not suggested by the use of either component individually, nor by the teaching of Yumibe, et al.

The synergistic effect of the combination of claim 4 amended herein is clearly shown by the data presented in Table 13 of the present application. In Table 13, the beta-lactam compound is the compound 56 of Tomiyama, et al., as recited in amended claim 4 and the HMG-CoA reductase inhibitor is atrovastatin.

As seen in Table 13, a combination prescription of compound 56 administered at 0.3 mg/kg/day with atrovastatin administered at 1 mg/kg/day lowered serum cholesterol in the test animals by 20.2%. In contrast, use of compound 56 alone at the same dosage lowered serum cholesterol by only 6.9% while atrovastatin alone at the same dosage lowered serum cholesterol by only 6.2%. Clearly when used together, the beta-lactam compound 56 and the HMG-CoA reductase inhibitor complement each other and produce a pharmacologically synergistic effect on the lowering of serum cholesterol. Such a synergistic effect between the beta-lactam and HNG-CoA reductase inhibitor is neither taught nor suggested by either Yumibe, et al., or Tomiyama, et al.

Although Yumibe, et al., disclose the use of an HMG-CoA reductase inhibitor with a beta-lactam compound, as has previously been pointed out, the beta-lactam of Yumibe, et al., is a different class of compound, i.e., an O-glycoside beta-lactam, having a different mode of activity than the beta-lactam of the present invention, which is a C-glycoside beta-lactam. Furthermore, nothing in Yumibe, et al., suggests a synergistic

activity between the O-glycoside beta-lactam of the reference and the HMG-CoA reductase inhibitor.

The only discussion in Yumibe, et al., of synergistic effect relating to the use of an HMG-CoA reductase inhibitor is the brief mention at column 2, lines 11-20 that "Combination therapy of an HMG-CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patient than either agent in monotherapy". However, neither the O-glycoside beta-lactam of Yumibe, et al., nor the C-glycoside beta-lactam of Tomiyama, et al., or the present invention are considered to be bile acid sequestrants, the beta-lactams and the bile acid sequestrants have completely different mechanisms of operation. Accordingly, the teaching of Yumibe, et al., relating to a synergistic effect of HMG-CoA reductase inhibitors and bile acid sequestrants is not relevant to the combination of the C-glycoside beta-lactam of compound 56 and an HMG-CoA reductase inhibitor and cannot be used to support the present obviousness rejection.

Furthermore, the fact that Yumibe, et al., teaches the combination of an O-glycoside beta-lactam with an HMG-CoA reductase inhibitor is not transferable to the Tomiyama, et al., teaching of the C-glycoside beta-lactam compound as there is nothing in Tomiyama, et al., to suggest a combination of that beta-lactam with another cholesterol inhibiting compound, nor that any appreciable synergistic effect would be expected.

In view of the foregoing, Applicants respectfully submit that it would not be obvious to one of ordinary skill in the art, knowing the action of the compounds of Yumibe et al. to expect the improvements exhibited by combining the fibrate-type compounds or cholesterol biosynthesis inhibitors of Yumibe et al. with the C-glycoside beta-lactams of Tomiyama et al. Because the actions of the beta-lactams of the respective references are different, although the ultimate effects are similar, Applicants respectfully submit that there is nothing in either reference to support the combination thereof as urged by the examiner and that a *prima facie* case of obviousness has not been established.

Accordingly, Applicants respectfully submit that the present rejection under 35 U.S.C. 103(a) is without support and should be withdrawn.

Although this Amendment is presented after a Final Office Action, it is submitted that it should be entered. The sole independent claim remaining in the application is independent Claim 4. Independent Claim 4 corresponds to previously presented Claim 15. As such, even if the Examiner believes that Claim 4 is unpatentable, it would be appropriate to enter Claim 4, at minimum, for purposes of Appeal.

The other remaining claims in the application are Claims 29-33, each of which is dependent from independent Claim 4. While each of these claims is newly presented herein, the remarks set forth above clearly delineate the support in the original

Specification for each and every recited limitation. As such, newly presented dependent Claims 29-33 do not raise issues requiring further consideration or search. If Claim 4 is allowable for the reasons set forth above, Claims 29-33 are allowable as well. As such, it is requested that even if the Examiner does not agree that Claim 4 as presented herein is allowable, this Amendment should be entered to simplify the issues that would be present on Appeal.

In view of the foregoing, Applicants respectfully submit that the claims as amended herein are allowable over the prior art, that this Amendment should be entered, and that a notice of allowance should be mailed.

Respectfully submitted,

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